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SPECIAL ARTICLE

THE ITALIAN CONSENSUS CONFERENCE ON PAIN IN NEUROREHABILITATION - PART II

Headache, low back pain, other nociceptive and mixed pain conditions in neurorehabilitation.

Evidence and recommendations from the Italian Consensus Conference on Pain in Neurorehabilitation

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ABSTRACT

Pain is a disabling symptom and is often the foremost symptom of conditions for which patients undergo neurorehabilitation. We systematically searched the PubMed and Embase electronic databases for current evidence on the frequency, evolution, predictors, assessment, and pharmacological and non-pharmacological treatment of pain in patients with headache, craniofacial pain, low back pain, failed back surgery syndrome, osteoarticular pain, myofascial pain syndrome, fibromyalgia, and chronic pelvic pain. Despite the heterogeneity of published data, consensus was reached on pain assessment and management of patients with these conditions and on the utility of a multidisciplinary approach to pain therapy that combines the benefits of pharmacological therapy, physiotherapy, neurorehabilitation, and psychotherapy. We of the Italian Consensus Conference on Pain in Neurorehabilitation (ICCPN) suggest a need to conduct randomized controlled trials on the efficacy of pain treatments and their risk-benefit profile for the conditions we have reviewed.

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Key words: Arthralgia - Facial pain - Failed back surgery syndrome - Fibromyalgia - Headache - Low back pain.

Pain is a disabling symptom that is often the foremost symptom of conditions for which patients undergo neurorehabilitation. This is further confirmed by the International Classification of Functioning, Disability and Health (ICF) that includes pain in some categories as to Body Functions (code b280-sensation of pain; code b289-sensation of pain, other specified and unspecified; code b298-sensory functions and pain, other specified; code b299-sensory functions and pain, unspecified).

Consistent with the aims of the Italian Consensus Conference on Pain in Neurorehabilitation (ICCPN), this article reports current evidence and criteria for good clinical practice in pain epidemiology, impact, evaluation, prognosis and treatment for the following clinical conditions: headache and craniofacial pain (CFP), low back pain (LBP) and failed back surgery syndrome (FBSS), osteoarticular pain (OP), myofascial pain syndrome (MPS) and fibromyalgia (FM), and chronic pelvic pain (CPP). While only some of these conditions are treated in neurorehabilitation, because of their epidemiological impact, they are frequent comorbidities in patients with neurological diseases.

CFP

Primary headache (PH) accounts for the majority of headache complaints in young people and adults; therefore, it should be evaluated in non-aged patients undergoing rehabilitation and in all patients undergoing rehabilitation for conditions that may cause secondary CFP. Appropriate assessment of the pain component of the disease, as well as co-existing PH, may aid in improving a patient's psychophysical well-being, promote adherence to the neurorehabilitation program, and potentially enhance treatment outcome. Indeed, rehabilitation outcome may be limited by the psychological disorders (*i.e.*, anxiety and/or depression) that are often associated with pain and that will need to be assessed. Although chronic pain syndromes in any patient should be evaluated to relieve possible sources of suffering, complaints not strictly related to the condition for which the patient is under therapy are often neglected.

LBP and FBSS

LBP and FBSS carry a significant socioeconomic burden in terms of loss of productivity, prolonged disability, and medical care costs or indemnity payment. Because different pathophysiologic mechanisms, as well as different types of pain may co-occur in the same patient, it is important to identify and treat them with pharmacological and non-pharmacological therapies in a multidisciplinary approach to reduce pain and improve disability.

OP

OP frequently diminishes quality of life (QoL) and functional profile in patients with neurological diseases. Secondary OP in neurological disorders may lead to reduced or increased muscular activity, altered motor control, use of orthoses or rehabilitation devices, as well as overuse of unaffected limbs.

MPS and FM

MPS is characterized by acute or chronic regional muscle pain in single or multiple regions (trigger points) within taut muscle bands. MPS manifests with stiffness and local twitch response when stimulated by digital pressure or located needling and generates local or referred pain.[1] FM is a central pain disorder that arises from a dysfunctional pain modulation system characterized by widespread tenderness often accompanied by sleep disturbance, fatigue, cognitive dysfunction, dysesthesia, irritable bowel, and mood disturbances. Recent evidence suggests that peripheral nerve involvement may coexist in some patients.[2, 3] FM is comorbid with other somatic symptom disorders, associated with psychological illness, and strongly influenced by social factors.[4]

CPP

CPP is a complex syndrome that comprises different pathological conditions with different treatment strategies. It is defined as non-cyclic pain lasting more than 6 months, apparently originating from the pelvic area and perceived as a sensory and emotional experience. It affects 15-20% of women of reproductive age. CPP is difficult to identify and treat, making its management often frustrating both for patients and clinicians. Due to its difficult diagnosis, it is the reason for 20% of diagnostic laparoscopies and 12-16% of hysterectomies, which in-

cur considerable medical costs.[5] The prevalence of CPP is 38/1000 in women aged between 16 and 73 years, similar to the rates for asthma (37/1000) or chronic LBP (41/1000).[6] CPP is more common in persons between 26 and 30 years of age. No difference in demographic characteristics was found between CPP patients and controls.

Materials and methods

The methodology of the ICCPN was based on the Italian guidelines for organizing a consensus conference, the Italian guidelines on stroke (Stroke Prevention and Educational Awareness Diffusion) and the Consensus Conference on neuropsychological rehabilitation in adult patients.[7] The ICCPN task force was composed of a promoter committee, a technical-scientific committee and a jury.[7] The topics of the ICCPN were divided into 27 working groups, which were incorporated into seven main paragraphs, three of which dealt with general issues and the remaining four dealt with specific clinical conditions that may be encountered in the neurorehabilitation setting.[7] The strength of recommendations was scored according to a scale ranging from A to good practice point (GPP) and is reported in parentheses after each recommendation.[7] For each condition mentioned above, we systematically searched the PubMed and Embase electronic databases using the following keywords, their corresponding MeSH terms (when available), and all their possible combinations for original research studies published from 1983 to 2013. Headache and CFP: primary headaches, tension-type headache, migraine, orofacial pain, facial pain, facial neuralgia, trigeminal neuralgia, temporomandibular disorder, pain measure, rehabilitation, neurorehabilitation, pharmacological treatment, non-pharmacological treatment, psychotherapy, relaxation therapy, manual therapy, physical therapy, osteopathic manipulative treatment, chiropractic treatment, orthodontic treatment, physiotherapy, acupuncture, surgical therapy, neuroablative therapy, local therapy, anesthetic block, herbal extracts, botulinum toxin, guidelines; LBP and FBSS: LBP, FBSS, diagnosis and examination, cost of illness, epidemiology, pain, nociceptive pain, neuropathic pain, myofascial syndrome, visual analogue scale, neuropathic pain diagnostic questionnaire, pain therapy, analgesic drugs, rehabilitation; OP: musculoskeletal pain, rehabilitation, shoulder pain, central nervous diseases; MPS and FM: MPS, myofascial pain treatment, myofascial pain diagnosis, myofascial pain therapy, myofascial pain exercise, fibromyalgia, fibromyalgia syndrome, fibromyalgia pain, fibromyalgia diagnosis, fibromyalgia treatment, fibromyalgia therapy, fibromyalgia exercise; CPP: interstitial cystitis, endometriosis, irritable bowel syndrome, vulvodynia. The search was updated to 2015 and selected papers were added to the review. In those fields with few good quality clinical studies, we chose a mixed approach, namely, a review of published studies identified through searching the PubMed and Embase databases, the grey literature, and a consensus conference to obtain recommendations from clinical evidence and expert opinion.

Results and recommendations

Question 7.1. Which are the classification criteria for headache, craniofacial pain, low back pain, osteoarticular pain, myofascial pain, fibromyalgia, and chronic pelvic pain, and what is the epidemiological impact of these conditions in neurorehabilitation?

Headache and CFP

We recommend reference to the International Headache Society diagnostic guidelines, which represent the gold standard for classifying headache and craniofacial pain subtypes.[8, 9]

LBP and FBSS

LBP is defined as pain originating from the lower margin of the twelfth ribs to the lower gluteal folds; it is classified as acute (<4 weeks), sub-acute (4 weeks to 3 months) or chronic (>3 months). Although LBP etiology is known in only 5-15% of cases, different pathophysiologic mechanisms may coexist, leading to inflammatory-nociceptive, neuropathic or central-dysfunctional pain.[10] Chronic LBP should be considered a mixed pain syndrome involving both nociceptive and neuropathic mechanisms. Nociceptive pain may be identified in 50-70% of LBP patients; the causes include lumbar intervertebral disc impairment, facet or sacroiliac joint disease, ligament injury or muscle tear. Neuropathic pain is present in 5-15% of LBP cases. It usually results from compressive or non-compressive lumbar radiculopathy,

leading to sciatic pain or neurogenic claudicatio. Dysfunctional pain is reported to occur mostly in chronic LBP with/without other pain syndromes, such as FM or chronic widespread pain, and changes in pain perception or body schema. Finally, a small percentage of patients (one out of thousands) report pain secondary to gastrointestinal, kidney or aortic diseases.[11]

FBSS refers to a broad spectrum of conditions characterized by persistent or recurrent LBP, with or without sciatic pain, as a result of one or more spinal surgery procedures. Different types of pain can coexist, leading to mixed pain syndrome also in FBSS. The radicular component may be secondary to inadequate surgical decompression, persistent foramen stenosis, epidural fibrosis or recurrent disc herniation.[12] It has been suggested that if pain appears acutely after surgery, the cause may be due to nerve root damage, while pain localized to the lumbosacral region is more indicative of nociceptive causes.[12]

We refer interested readers to an ICCPN paper on the clinical and instrumental tools for distinguishing the nociceptive and neuropathic components of mixed pain conditions.[13]

OP

OP is the leading complaint in several orthopedic, rheumatologic, and internal medicine conditions. Here we will focus on common neurological conditions. OP may be one of the many complications of acute phase stroke.[14] Shoulder pain on the paretic side, associated with complex regional pain syndrome (CRPS) and knee pain on either the affected or the unaffected side are frequent in stroke patients.[15-17] The OP prevalence in Parkinson's Disease is 46%; the most frequent forms are LBP, especially in patients with Pisa syndrome, shoulder pain and knee pain.[18] Spinal fractures secondary to osteoporosis may occur in Parkinson's disease, and therefore should be considered in patients with acute back pain.[19] OP may affect over 50% of patients with spinal cord injury (SCI),[20] with shoulder pain related to arthrosis and overuse syndromes being reported as the main OP type.[21, 22] LBP is also common in SCI patients, but it frequently has a neuropathic component.More than 50% of multiple sclerosis patients have pain, but there is a scant literature about OP in this condition, with LBP prevalence reported to range from 10 to 16%.[23, 24] The different types of pain associated with stroke, SCI, and multiple sclerosis are discussed in more detail in another ICCPN article,[24] to which we refer the interested reader.

MPS and FM

It is reported that 15% of routine medical clinic visits and 85% of pain clinic consultations are for soft tissue pain.[25] The prevalence of MPS in patients with regional pain ranges from 30 to 93%. The muscles most frequently affected by MPS are the trapezius, levator scapulae, infraspinatus, and scalene muscles.[1] The best estimate for the incidence of FM is 2 to 4% in any population, regardless of country of origin.[3]

CPP

Urological, gynecological, gastrointestinal, musculoskeletal, and neurological causes may contribute to

Table I.—*The terminology of chronic pelvic pain.*

Term	Definition
Vulvodynia	Vulval discomfort, often described as burning pain, with no visible findings, or a specific, clinically identifiable neurological disorder
Vestibulodynia	Provoked pain localized to the vestibule region, with pain experienced on sexual and non-sexual touch
Dyspareunia	Pain during sexual intercourse at the point of penetration or deep in the vagina
(Dysaesthetic) penoscrotodynia	The male counterpart of vulvodynia, *i.e*., pain or discomfort involving the penis and/or the scrotum
Red scrotum syndrome	Localized painful reddening of the scrotum (similar to focal erythromelalgia?)
Vaginismus	Tightening of the pelvic floor muscles
Pelvic muscles hyperactivity	Pathological hyperactivity of pelvic floor muscles
Overactive bladder	Urgency, with or without urge incontinence, and daytime and/or night-time frequency, with no obvious infection or pathology
Interstitial cystitis/ bladder pain syndrome	Suprapubic pain related to bladder filling with other symptoms (*e.g*., increased daytime and night-time frequency) with no proven urinary infection or other obvious pathology
Chronic prostatitis/ chronic pelvic pain syndrome	Genitourinary pain with or without voiding symptoms in the absence of urinary infection or other identifiable causes
Persistent genital arousal disorder	Involuntary genital and clitoral arousal that: 1) persists for an extended period of time; 2) does not go away following one or more orgasms; 3) is unrelated to subjective feelings of sexual desire; 4) is reported as intrusive, unwanted, or distressing

CPP, including endometriosis, pelvic inflammatory disease, painful pelvic adhesion syndrome, interstitial cystitis, irritable bowel disease, proctosigmoiditis, ulcerative colitis, colon diverticulosis, tumors, pelvic MPS, and pudendal neuropathy. CPP represents an umbrella term that encompasses nociceptive, neuropathic, and visceral pain, diseases associated with pelvic muscle hyperactivity, and complex conditions such as restless genitalia syndrome.[26-28] The main terms and syndromes associated with CPP are reported in Table I. Coexistent FM and psychological changes secondary to CPP may contribute to CPP and its burden.

Recommendation 7.1.1. The International Headache Society diagnostic guidelines should be used for classifying headache and craniofacial pain subtypes (B).

Recommendation 7.1.2. Osteoarticular pain and low back pain should be assessed in patients with stroke, Parkinson's disease, spinal cord injury, and multiple sclerosis (GPP).

Recommendation 7.1.3. Better classification of chronic pelvic pain, which encompasses nociceptive, neuropathic, and visceral pain, as well as pelvic muscle hyperactivity and complex conditions, is recommended (GPP).

Question 7.2. Are there methods or standardized criteria for the assessment of pain in headache, craniofacial pain, low back pain, osteoarticular pain, myofascial pain, fibromyalgia, and chronic pelvic pain?

Headache and CFP

The visual analogue scale (VAS), the numerical rating scale (NRS), and their variants can be used for grading pain intensity in headache and CFP. The Migraine Disability Assessment score (MIDAS) has been proposed and validated as a simple self-administered questionnaire to quantify the degree of disability due to headache.[29] The clinical usefulness of MIDAS is limited by the lack of items investigating other conditions, such as anxiety and mood disorders that should be evaluated in patients with pain. Headache patients are usually asked to keep a monthly headache diary for reporting pain intensity (0=no pain, 1=mild, 2=moderate, 3=severe), headache frequency and duration, aura, symptoms associated with headache, as well as drug intake and efficacy, the last being indirectly measured by pain relief or cessation.[30-32]

LBP and FBSS

The etiology of LBP is multifactorial, and its diagnosis is made by exclusion of other conditions.[33] Guidelines suggest evaluating the patient's medical history and physical examination to identify the underlying causes of LBP, the presence of neurological symptoms and signs, and the so-called red flags, which include signs, symptoms or risk factors that suggest the presence of a severe disease, such as tumor, fracture, infection, spinal cord stenosis, abdominal aortic aneurysm. In patients with acute LBP, neuroimaging should be performed only when red flags and/or neurologic symptoms and signs are present. Unexplained persistence of LBP>2-3 months is another red flag that should prompt investigation of pain etiology. Yellow flags are risk factors for LBP chronicization and long-term disability; they include psychological (*i.e*., fear avoidance behavior, unrealistic treatment expectations, mood disturbances), and social/environmental factors (*i.e*., poor job satisfaction, conflicting relationships at work, insurance issues).[34] LBP intensity is measured with generic scales commonly used for evaluating other types of pain, such as the VAS and the NRS. Disability secondary to LBP should be measured with a specific scale, including the Oswestry Disability Index and the Roland Morris Disability Questionnaire.[33]

Detailed evaluation of patients with FBSS is key to obtain valuable information on the etiology of persistent or recurrent pain, the patient's psychosocial status, comorbidities, and previous interventions and/or therapeutic approaches. Red and yellow flags should be carefully looked for, and neuroimaging, electrodiagnostic and/or laboratory tests performed as needed.[35]

OP

OP intensity can be measured with generic scales such as the VAS and the NRS. There are a number of scales that evaluate functioning and disability in patients affected by OP. Some scales (*e.g*., the Pain Disability Index) are generic, while others are specific for a single type of OP (*e.g*., the Neck Disability Index). Rating scales that have been translated and validated in the patient's language should be used.[36, 37] Radiologic and laboratory examinations are helpful for exploring the cause of OP and to guide pharmacological and non-pharmacological treatment decisions.

MPS and FM

The diagnosis of MPS is based on the identification of trigger points in the taut band by palpation of sensitive nodules to elicit local twitch response and specific patterns of pain associated with each trigger point.[1] The American College of Rheumatology (ACR) 2010 preliminary diagnostic criteria for diagnosing FM consists of two scales, the Widespread Pain Index (Part 1) that assesses pain at 19 sites depicted on a body diagram, and the Symptom Severity Scale (Part 2).[38] With the 2011 modification of the ACR 2010 criteria, the physician's estimate of the extent of somatic symptoms was substituted by the sum of three specific self-reported symptoms.[39]

CPP

Accurate clinical history taking is important in CPP because approximately 30% of women with CPP develop this condition following pelvic inflammatory disease, probably as a result of permanent abnormalities of the uterus, fallopian tube, and/or ovaries.[27, 40] Pain intensity should be rated with the VAS or NRS, pain distribution should be accurately assessed, and information on sexual functioning, disability, and previous failed treatments collected.[27] A recent study suggested that approximately one third of CPP patients may suffer from neuropathic pain,[41] according to a neuropathic pain screening tool.[13] Neurological examination should be performed whenever possible. Potentially treatable causes of CPP should always be sought and identified, and instrumental examination, such as transvaginal ultrasonography or pelvic magnetic resonance imaging (MRI) should be performed accordingly.[27, 42] Electrodiagnostic assessment of the pelvic floor is recommended when a neuropathic cause of CPP is suspected.[13]

Recommendation 7.2.1. The visual analogue scale and the numerical rating scale should be used for the assessment of pain intensity in headache, craniofacial pain, low back pain, osteoarticular pain, myofascial pain, fibromyalgia, and chronic pelvic pain (B).

Recommendation 7.2.2. Generic or specific disability scales should be used to explore the impact of headache pain, craniofacial pain, low back pain (B), osteoarticular pain, myofascial pain, fibromyalgia, and chronic pelvic pain (GPP).

Recommendation 7.2.3. Red flags indicating the possible presence of a severe disease, and yellow flags signaling a risk for pain chronicization should be assessed in patients with low back pain and failed back surgery syndrome (B).

Recommendation 7.2.4. The 2010 American College of Rheumatology criteria are recommended for the diagnosis of fibromyalgia (B).

Question 7.3. What is the impact of headache, craniofacial pain, low back pain, osteoarticular pain, myofascial pain, fibromyalgia, and chronic pelvic pain on neurorehabilitation?

Headache and CFP

We found no useful data on this issue.

LBP and FBSS

Chronic LBP has a significant socioeconomic impact in terms of lost productivity, prolonged disability, and increased costs for medical care or indemnity payment.[43] Among active workers aged 45-65 years, LBP is one of the most frequent causes of job loss, diminished QoL and mental well-being.

Patients with FBSS experience higher levels of pain, have higher rates of absence from work, and show lower QoL scores when compared with patients suffering from other chronic pain conditions.[12, 44] The annual cost in U.S. dollars for medical treatment of FBSS is estimated at $18,883 per patient in the United States.[35] Based on these figures, strategies to prevent and satisfactorily manage FBSS are recommended.

OP

OP is a leading cause of disability and diminished QoL and a common complaint in patients with neurological conditions such as stroke.[44, 45] However, reliable data on the impact of OP on neurorehabilitation procedures are scant because of contrasting evidence and the presence of mixed pain conditions.[13, 14, 46]

MPS and FM

To the best of our knowledge, there is no evidence on the impact of MPS or FM on neurorehabilitation proce-

dures. In these conditions, however, pain intensity may be related to health status and mediate the association between physical activity and daily functioning.[47, 48]

CPP

CPP has a significant impact on daily functioning, work, and QoL. CPP patients often present with psychological comorbidities, sleep disorders, and fatigue. In a 1992 UK survey, the costs related to CPP were estimated to be approximately £180 million.[49] Data on the burden of CPP on neurorehabilitation are lacking.

Recommendation 7.3.1. Studies on the impact of headache, craniofacial pain, low back pain, osteoarticular pain, myofascial pain, fibromyalgia, and chronic pelvic pain on neurorehabilitation are recommended (GPP).

Question 7.4. Are there predictive factors for the development of headache, craniofacial pain, low back pain, osteoarticular pain, myofascial pain, FM, and chronic pelvic pain?

Headache and CFP

The literature on this issue is very scant. Headache is reported in 10-13% of stroke patients, but no risk factors have been identified.[50, 51] Preexisting migraine may reappear after cognitive function recovery in patients with severe brain injury, but the mechanisms underlying this phenomenon are unclear.[52]

LBP and FBSS

Demographic risk factors for the onset and the clinical course of LBP include age, gender, body-mass index (BMI), and educational level. The incidence of LBP is highest in the third decade of life and its prevalence increases with age up to 60-65 years. Chronic LBP is reported to be more frequent in women, but the data are contradictory.[43] A stronger correlation between LBP and a high BMI (>30) has been reported in women than in men. Low educational levels, longer duration of each episode, and worse outcome have all been linked to the high prevalence of LBP. The few studies that have explored the correlation between genetic factors and lumbar disc degeneration have reported only preliminary data. Mechanical overload at the lumbar level and other occupational risk factors (*e.g.*, stress, rotation or sudden movements of the spinal column, whole-body vibration) appear to be a prognostic factor for LBP chronicity. Reduction or avoidance of these factors could prevent LBP recurrence after an acute attack. In contrast, prolonged sitting or sedentary lifestyle does not seem to consistently predict LBP.[53] As mentioned above (see question 7.2), yellow flags should always be assessed in LBP patients.[34]

Risk factors for FBSS include psychological and socio-economic variables, repeated surgery, inadequate surgical technique or approach to the wrong vertebral level (2.1-2.7% of cases), surgical complications (*e.g.*, infection, hematoma, LBP recurrence after discectomy (15% of cases), epidural fibrosis (20-36% of cases), and myofascial pain resulting from prolonged dissection of the paraspinal muscles during surgery.[35] It should be noted that the success rate of the first spinal surgical procedure is approximately 50%, but it falls to 30%, 15%, and 5% after the second to fourth operations, respectively.[35]

MPS and FM

Both mechanical (*i.e.*, structural, postural and ergonomic) and non-mechanical (*i.e.*, medical) causes may exacerbate MPS and FM and negatively influence pain treatment. In particular, medical factors that contribute to pain persistence include nutritional deficits (*e.g.*, vitamin B12, vitamin D, iron), hormonal dysfunctions (*e.g.*, thyroid diseases, growth hormone deficiency), and infections (*e.g.*, enterovirus, Lyme disease, recurrent candida albicans).[54] Lipid and lipoprotein levels, salivary cortisol, and anxiety levels were also found to be associated with MPS.[55] Other risk factors for FM are female sex and psychological distress.[56]

CPP

Depression, anxiety, low sociocultural status and past history of physical or sexual abuse have been reported as risk factors for CPP, but the data on this topic are scanty.[40, 57]

Recommendation 7.4.1. Studies on risk factors and predictors for headache, craniofacial pain, low back pain, osteoarticular pain, myofascial pain, fibromyalgia, and chronic pelvic pain in neurorehabilitation are recommended (GPP).

Question 7.5. What is the evidence for pharmacological and non-pharmacological treatments of headache pain, craniofacial pain, low back pain, osteoarticular pain, myofascial pain, fibromyalgia, and chronic pelvic pain?

Headache and CFP

The Italian Society for the Study of Headache (SISC) provides pharmacological guidelines for PH.[31] The results from our search for more recent evidence show that the SISC guidelines appear up-to-date; therefore, we can recommend their use for guiding pharmacological and non-pharmacological treatment of PH. Recently published studies documented the role of meditation therapy,[58] mindfulness-based stress reduction,[59] acceptance and commitment therapy,[60] and yoga,[61] for PH, and neurofeedback therapy for post-stroke and post-traumatic headache and PH.[62]

Non-neuropathic orofacial pain may be a manifestation of various different diseases, including periodontal, vascular, sinus bone alterations, cancer or temporomandibular disorder (TMD),[63] the last being the second most common cause of oral pain after odontogenic causes and potentially responsible for persisting/chronic pain.[64] These conditions may be accompanied by psychological distress and reported pain of cervical origin despite normal laboratory or radiological findings, or accompany chronic pain due to other sources. To date there are no data supporting specific recommendations on pharmacological treatment of non-neuropathic orofacial pain. Non-pharmacological strategies for TMD include occlusal splint, physical therapy, manual therapy (MT), and acupuncture,[65] while the evidence for orthodontic treatment is poor.[66] Non-significant short-term improvements in pain intensity and joint range were reported in a randomized controlled trial (RCT) exploring MT and home exercise programs in patients with TMD.[67] Therapeutic exercises combined with conservative care appear to be effective in treating TMD.[68] A RCT involving patients with cervicogenic headache and TMD showed that orofacial MT, in addition to usual cervical care, has a long-term beneficial effect on cervical movement in comparison to the latter alone.[69] Therefore, TMD should be sought when examining patients with cervical disorders or pain. Systematic reviews on the effectiveness of physiotherapy for TMD are inconclusive because of the poor quality of the studies on this therapeutic approach. Multidisciplinary interventions for TMD should include surgical procedures when conservative treatments fail.[70] A meta-analysis showed that psychosocial interventions do appear not to be superior to usual treatment for myofascial TMD pain.[71] Acupuncture was found to have short-term efficacy in relieving TMD pain, but the results were not conclusive due to the limited number of patients evaluated.[72]

For the pharmacological treatment of trigeminal neuralgia (TN), we recommend reference to the European Federation of Neurological Societies guidelines.[73] RCTs offer insufficient evidence on non-antiepileptic drugs in TN.[74] For refractory TN, botulinum neurotoxin type A (BoNT-A) may represent an effective treatment, with response rates up to 85%, similar to those achieved with carbamazepine/oxcarbamazepine, a reduction in mean duration of pain of 105 days,[75] level B evidence for TN,[76] and the additional indication of hemifacial spasm.[77]

Other topical treatments, which include the 5% lidocaine patch and the 8% capsaicin patch, play a role in relieving neuropathic pain,[78] but there is no evidence to date for their use in orofacial pain and TN.

There is no conclusive evidence for the role of local drug infiltration or arthrocentesis associated with injection of low- or high-molecular-weight hyaluronic acid or cortisone in osteoarthritic TMD.[79] The quality of the evidence on interventional procedures in TN is low. A prospective non-randomized study showed that retrogasserian rhizolysis with glycerol and percutaneous radiofrequency thermocoagulation can induce a moderate reduction in pain in TN.[80] The combination of continuous and pulsed radiofrequency produced better results than continuous radiofrequency alone, reduced the duration of treatment, and resulted in long-lasting effects.[81]

The features of glossopharyngeal neuralgia (GN) pain are similar to those of TN. However, pharmacological treatments for TN are largely ineffective for GN and invasive procedures are frequently required.[82] Finally, there are no conclusive data regarding facial neuralgia (*i.e.*, facial pain other than typical TN) and Bell's palsy.

LBP and FBSS

The treatment of acute and chronic LBP should be well differentiated because they are two very different clinical situations. Acute LBP requires mainly symptomatic treatment, counseling and prevention. Subacute and chronic LBP, because they are influenced by physical dysfunctions, patient expectations, behavioral changes, and so-

cial interactions, require a multimodal multidisciplinary approach based on a biopsychosocial model of disease where rehabilitation can play a major role. Chronic LBP treatment should be aimed at reducing pain and disability and improving QoL. Though many treatment options are available for LBP, their efficacy is often very limited and the quality of evidence is low.[10]

The following two paragraphs briefly summarize the main pharmacological options for LBP. Paracetamol should be considered as first-line treatment for LBP due to its good side-effects profile; however, a recent review reported no statistically significant difference between paracetamol and other drugs.[10] A systematic review demonstrated the short-term efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs) with no difference between single active principles in this drug group;[83] hence, they should be used as second-line treatment in acute and chronic LBP. Tramadol is slightly better than placebo for LBP and related disability; its effectiveness is comparable to that of NSAIDs and weak opioids,[10] making it a third-line therapeutic option in LBP. The use of opioids in LBP is controversial because of their limited efficacy in comparison to placebo or non-opioid analgesics.[78] Opioids should be considered only as a short-term third-level option in patients with severe and disabling pain unresponsive to paracetamol, NSAIDs, and tramadol, or in patients with moderate-to-severe pain but at high risk for NSAID complications.[78] Long-acting opioids can be considered in patients with chronic LBP, while short-acting opioids are preferable in acute LBP.[83] Tricyclic antidepressants were found to be slightly more effective or ineffective versus placebo. While they are not recommended as first-line treatment for chronic LBP,[10] they can be considered in refractory patients. RCTs demonstrated no beneficial effect of systemic corticosteroids versus placebo in patients with LBP, either associated or not with radicular pain;[83] therefore, treatment with these drugs is not recommended.

There is no evidence that local anesthetic injection, with or without corticosteroids, chemical irritants, intramuscular BoNT-A injection, intradiscal or epidural injection of steroids or proteolytic enzymes may be effective in LBP.[10] Recent guidelines on interventional procedures for neuropathic pain do, however, give weak recommendation for the use of steroid injections for radiculopathy, which may coexist with LBP.[78]

Despite its low evidence of efficacy, surgical or percutaneous vertebral arthrodesis may be considered in LBP patients who do not respond to a combination of conservative treatments for severe pain, disability or spinal degenerative disease. Arthrodesis does not appear to be any more effective than conservative approaches.[10, 84] In cases of LBP and radiculopathy secondary to herniated disc, microdiscectomy is preferable over other surgical procedures because it is less invasive and has lower failure rates.[10]

A variety of physical and exercise approaches have been reported to reduce LBP by less than 30% and improve function by less than 20% overall. The evidence for their effectiveness is limited owing to their inclusion as a part of multimodal rehabilitation programs, which precludes thorough evaluation of the efficacy of each therapeutic component.[10] Patients with acute LBP are usually advised to be active, but the relationship between physical activity and disability in acute LBP is weak.[85] Educational booklets, back school programs, and behavioral therapy may be useful to ameliorate QoL, reduce the risk of LBP recurrence, and improve mood in acute, subacute, and chronic LBP, but the evidence is scanty and there are no data on patient selection criteria that predict who might be best responders to such treatments.[33] Data on spinal manipulations and recommendations from different guidelines are contrasting. Transcutaneous electrical nerve stimulation (TENS) is often used in the treatment of chronic LBP, but because the evidence for its efficacy is very low, TENS is not recommended for the treatment of LBP.[78, 86] Other physical therapies include therapeutic ultrasound and laser therapy.[87] One systematic review demonstrated that acupuncture, a popular complementary treatment, may have a favorable effect on self-reported pain and functional limitations in LBP patients, but the results need to be interpreted with caution because of the heterogeneous study population and low methodological quality.[88]

There are few RCTs and guidelines on the treatment of FBSS, a chronic condition that requires individualized multidisciplinary treatment to recover function, improve QoL, and develop coping strategies to pain.[35] Commonly prescribed drugs for FBSS include paracetamol, NSAIDs, COX-2 inhibitors, tramadol, opioids, and other drugs for neuropathic pain (*i.e.*, gabapentin, antidepressants) despite the lack of RCTs testing their efficacy in this condition.[35] Physical exercise and rehabilitation are commonly prescribed for FBSS patients, who often develop deconditioning with muscular weakness and spinal instability, but the evidence for their effectiveness

is lacking. Behavioral therapy, because of the primary role psychological factors play in the chronicization of pain in FBSS, may be helpful in some cases. While invasive procedures including surgery are used for diagnostic and therapeutic purposes, the risk of exacerbating pain needs to be adequately weighed along with other factors. Based on the evidence from moderate-to-high quality RCTs, spinal cord stimulation (SCS) should be considered in FBSS and LBP refractory to conservative management.[78, 89] High frequency, burst, and adaptive stimulation are new SCS modalities that seem to be more effective than conventional SCS, but their role in FBSS has not been consistently explored.[78]

OP

A thorough review of currently available pharmacological and non-pharmacological therapies for OP and their evidence levels is beyond the scope of this article. Pharmacological and non-pharmacological treatment of nociceptive pain, including opioids, invasive procedures, physical therapy, and psychotherapies have been examined in detail elsewhere. [78, 90] Patients with neurological conditions may experience secondary OP (*e.g.*, shoulder pain after stroke is common). Detailed recommendations for the treatment of OP associated with spasticity, stroke, multiple sclerosis, spinal cord injury, and cerebral palsy, Parkinson's Disease, motor neuron disease, dementia, severe acquired brain injury, disorders of consciousness, (neuro) oncology and neuroinfectious diseases are reported in other ICCPN articles.[24, 91]

MPS and FM

Pharmacological therapies proposed for MPS include trigger point injections, spray and stretch with vapocoolants, topical analgesics, glucosamine and methylsulfomethane, NSAIDs, and BoNT-A injections;[1] however, no conclusions on the efficacy of the majority of these treatments can be drawn due to the low quality of studies. Numerous drugs are indicated for the treatment of pain in FM, including pregabalin, gabapentin, anticonvulsants, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors (SNRIs), norepinephrine reuptake inhibitors (NRIs), tricyclic antidepressants, dopaminergic agents, tramadol, opioids, tropisetron, nabilone, sodium oxybate, central muscle relaxants (*i.e.*, cyclobenzaprine, carisoprodol, tizanidine, methocarbamol, and metaxalone) alone or in combination with analgesics (*i.e.*, paracetamol, NSAIDs).[92-94] A very recent meta-analysis on the pharmacological treatment of FM explored as outcome measures not only pain, but also an extensive list of symptoms that included pain, tenderness, fatigue, multidimensional function, sleep disturbances, depression, cognitive dysfunction, stiffness, and anxiety. While treatment with most pharmacological classes resulted in a reduction in pain and/or fatigue, very few have demonstrated improvement in other domains, and SNRIs and NRIs were the only drug classes possibly associated with overall treatment response.[95]

There is a wide variety of non-pharmacological approaches to treating MPS and FM pain: ergonomics, traction, mechanical massage, fascial manipulation, whole-body vibration, chiropractic management, craniosacral therapy, aerobic exercise, stretching exercise, biofeedback, cognitive-behavioral therapy (CBT), acupuncture, dry needling, spa therapy, balneotherapy, hypnotherapy, yoga, ischemic acupressure or Shiatsu, hot and cold therapies (*i.e.* cold and hot packs, Whirlpool and Jacuzzi jet massaging therapy, Waon soothing warmth therapy), extracorporeal shock wave therapy, ultrasound therapy, Ga-Al-As laser therapy, electrotherapy (TENS, interferential therapy, FREMS therapy) and phonophoresis.[92, 96-101] A network meta-analysis showed that the benefits of pharmacological treatments in FM are of questionable clinical relevance, the evidence for benefits of non-pharmacological interventions is limited, and that the combination of pregabalin or SNRIs, as pharmacological interventions, and multicomponent therapy, aerobic exercise and CBT, as non-pharmacological interventions, seems most promising for the management of FM.[102] It is suggested that a multidisciplinary approach to FM should include education about the nature of disorder, counseling regarding the role of exercise, CBT, and pharmacological therapy as guided by the predominant symptoms that accompany pain (*e.g.*, SNRIs for comorbid depression or fatigue, pregabalin or gabapentin for comorbid anxiety or sleep disturbances) and the combined use of several classes drugs, including NSAIDs and paracetamol, while the use of opioids is often discouraged.[103]

CPP

Analgesics and drugs for neuropathic pain are commonly considered potential treatments for CPP, but pharmacological treatment guidelines for nociceptive and neuropathic pain are difficult to translate to this condition because few studies have investigated the use of these drugs in CPP.[78] For example, pregabalin, which is first-line treatment for neuropathic pain and demonstrated by RCTs as being effective for pain relief, was ineffective and associated with adverse effects in the only RCT involving men with chronic prostatitis/CPP.[104] CPP is a complex condition that comprises a heterogeneous array of clinical conditions with largely unknown pathophysiology (Table I). RCTs evaluating the use of antibiotics, α-blockers, anti-inflammatory and immune-modulating substances, bioflavonoids, hormonal agents, phytotherapeutics, neuromodulatory drugs, topical local anesthetics, agents that modify bladder function, pelvic floor physical treatment, muscle biofeedback, TENS, percutaneous tibial nerve stimulation, CBT, and acupuncture all failed to achieve a clear therapeutic benefit after a single treatment in CPP. The best evidence-based management strongly suggests a multimodal therapeutic approach that addresses the individual clinical phenotypic profile.[27, 105] Invasive procedures including bladder instillation therapy, peripheral nerve blocks, sacral neuromodulation, and other surgical procedures may be an effective choice, but because the overall evidence is limited, such interventions should be managed by a pelvic pain therapist within a framework of different therapeutic options.[106, 107] Pelvic floor musculature contracture can contribute to CPP. Since injection of BoNT-A acts on muscle hyperactivity and inhibits the release of peripheral neurotransmitters and inflammatory mediators from sensory nerves, it may be a promising strategy for this condition.[108] Preliminary studies show that BoNT-A injection in the pelvic floor muscle improves dyspareunia and decreases pelvic floor pressure, and that intravesical BoNT-A injection is useful in inflammatory bladder diseases, such as chemical cystitis, radiation cystitis, and ketamine-related cystitis.[109] Further research into the treatment of CPP is needed. By combining the data from RCTs with biomarker, genomic, and imaging studies, coupled with epidemiologic and symptom-based assessments, researchers can maximize the ability to probe the etiology and pathogenesis of this disease, and identify effective treatment.[110]

Recommendation 7.5.1. We recommend reference to the Italian Society for the Study of Headache guidelines for the pharmacological and non-pharmacological treatment of primary headaches (A).

Recommendation 7.5.2. Non-pharmacological strategies including manual therapy (D) and multidisciplinary approaches (GPP) should be considered for temporomandibular disorder.

Recommendation 7.5.3. We recommend reference to the European Federation of Neurological Societies guidelines for the pharmacological treatment of trigeminal neuralgia (A).

Recommendation 7.5.4. Botulinum neurotoxin type A injection is effective for the treatment of idiopathic trigeminal neuralgia and hemifacial spasm (B).

Recommendation 7.5.5. A multidisciplinary rehabilitation approach based on the biopsychosocial model of disease is recommended for the treatment of subacute and chronic low back pain and failed back surgery syndrome (GPP).

Recommendation 7.5.6. For the pharmacological treatment of low back pain, paracetamol should be considered as first-line, nonsteroidal anti-inflammatory drugs as second-line, and tramadol and opioids as third-line treatment (A). The drug dosage should be tailored to each patient, and the side-effects profile considered (GPP). Short-use of opioids is recommended (GPP). Tricyclic antidepressants and systemic corticosteroids should not be used in the treatment of chronic low back pain (B).

Recommendation 7.5.7. Among invasive procedures, steroid injections can be considered for radiculopathy coexisting with low back pain (B), microdiscectomy is preferable over other surgical procedures in the treatment of low back pain and radiculopathy secondary to herniated disc (C). Other surgical procedures can be considered only in patients who do not respond to a combination of conservative treatments and have severe chronic pain and disability (GPP).

Recommendation 7.5.8. Rehabilitation approaches have limited efficacy on low back pain and related disability; however, they should be considered in the multidisciplinary treatment of low back pain because of the absence of side effects (B). Transcutaneous electrical stimulation and other physical therapies are not recommended for low back pain (A).

Recommendation 7.5.9. Acupuncture has a beneficial effect on pain and functional limitations and should be considered in the multidisciplinary treatment of low back pain, but much work is still needed to improve the quality of studies on this topic (B).

Recommendation 7.5.10. Spinal cord stimulation should be considered for failed back surgery syndrome not responsive to less invasive treatments (B). Further research is recommended for this condition (GPP).

Recommendation 7.5.11. Botulinum neurotoxin type A injection can be considered for the treatment of myofascial pain syndrome in neck and head muscles (B).

Recommendation 7.5.12. A multidisciplinary approach, which includes pharmacological treatment with pregabalin/gabapentin, and/or serotonin norepinephrine reuptake inhibitors, and non-pharmacological strategies, such as aerobic exercise and cognitive-behavioral therapy, is recommended for the treatment of fibromyalgia (A). Other treatments for fibromyalgia that can be considered include tramadol, fluoxetine, massage therapy, and laser therapy (B), acupuncture and trigger point injection (C).

Recommendation 7.5.13. A multidisciplinary approach addressing the individual clinical phenotypic profile is recommended in the treatment of chronic pelvic pain (GPP).

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